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CASE REPORT

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Life After Tetra Hit: Anti-NMDAR Encephalitis After HSV Encephalitis in a NMOSD Coexistent with Sjögren's Syndrome

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ABSTRACT

Herpes simplex encephalitis (HSE) and anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis are associated entities. On the contrary, although both are autoimmune diseases, the association of neuromyelitis optica spectrum disorder (NMOSD) and anti-NMDAR encephalitis is not well explained. Herein, we present consecutively developed post-herpetic anti-NMDAR encephalitis in a patient with the coexistence of NMOSD and Sjogren syndrome. In our patient evaluation with MRI and clinical findings, the diagnosis of HSE after immunosuppressive drug application for NMOSD was made. Whereupon, HSE triggered NMDAR encephalitis. Many authors demonstrated the induction of anti-NMDAR encephalitis over herpes encephalitis with the presence of movement disorders, psychiatric manifestations, and cognitive dysfunction. In our patient, without biphasic disease activity; the persistence of symptoms, new MRI findings, and the positivity of anti-NMDAR antibody confirmed the anti-NMDAR encephalitis diagnosis. Our patient is a representative case mentioning the importance of close follow-up of a patient in neuroimmunology.

Keywords: Neuromyelitis optica spectrum disorder, herpes simplex encephalitis, anti-N-methyl-D-aspartate receptor encephalitis

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INTRODUCTION

Herein, we present consecutively developed post-herpetic NMDA encephalitis in a patient with the coexistence of NMOSD and Sjögren syndrome.

CASE

A 52-year-old otherwise healthy female patient with dry eyes and dry mouth presented to our clinic with a subacute onset back pain, paraparesis, and anesthesia under T2 level. Neurologic examination revealed severe paraparesis, bilateral hyperreflexia of the lower limbs, loss of sensation of light touch, heat, and pinprick below the T2 level. Magnetic resonance imaging of the spine revealed longitudinally extensive myelitis extending from the medulla oblongata to the lower thoracic segments with heterogeneous contrast enhancement (Figure 1. a, b). Brain MRI was unremarkable. We performed a diagnostic work-up for the etiology of transverse myelitis. Cerebrospinal fluid (CSF) analyses were done; glucose and protein levels were 66 mg/dl (serum: 121 mg/dl) and 342 mg/dl, respectively. CSF was negative for oligoclonal bands. Cytopathological examination revealed no atypical cells. The anti-aquaporin4 (anti-AQP4) antibody was 1/100 positive, and the myelin oligodendrocyte glycoprotein (MOG) antibody was negative. Anti-AQP4 positive neuromyelitis optica spectrum disorder (NMOSD) was our initial diagnosis. Apart from a mild increase in the erythrocyte sedimentation rate and C-reactive protein levels, her anti-Ro/SSA antibody and Schirmer test were positive, and salivatory gland biopsy showed grade 4 changes.

Highlights

- **Immunsuppresive treatments may trigger infections like Herpes simplex encephalitis (HSE).**
- **Anti-NMDAR encephalitis can be observed in NMOSD whether or not triggered by HSE**
- **NMOSD should be followed closely for treatment side effects and coexisting autoimmune diseases**

She was also found to be positive for HLA B51. Those two findings lead us to the diagnosis of a coexisting Sjögren`s disease. While she did not respond to seven-days-intravenous methylprednisolone treatment, she had mild improvement after plasma exchange. For maintenance therapy, she received a cyclophosphamide regimen, but due to difficulty of use, we switched to azathioprine (AZA) and hydroxychloroquine. One month after the symptom onset, her symptoms mildly improved to mild paraparesis.

One month later, she was admitted to our emergency service with fluctuating and altered mental status with memory impairment. Neurologic examination revealed partial cooperation, place, and time

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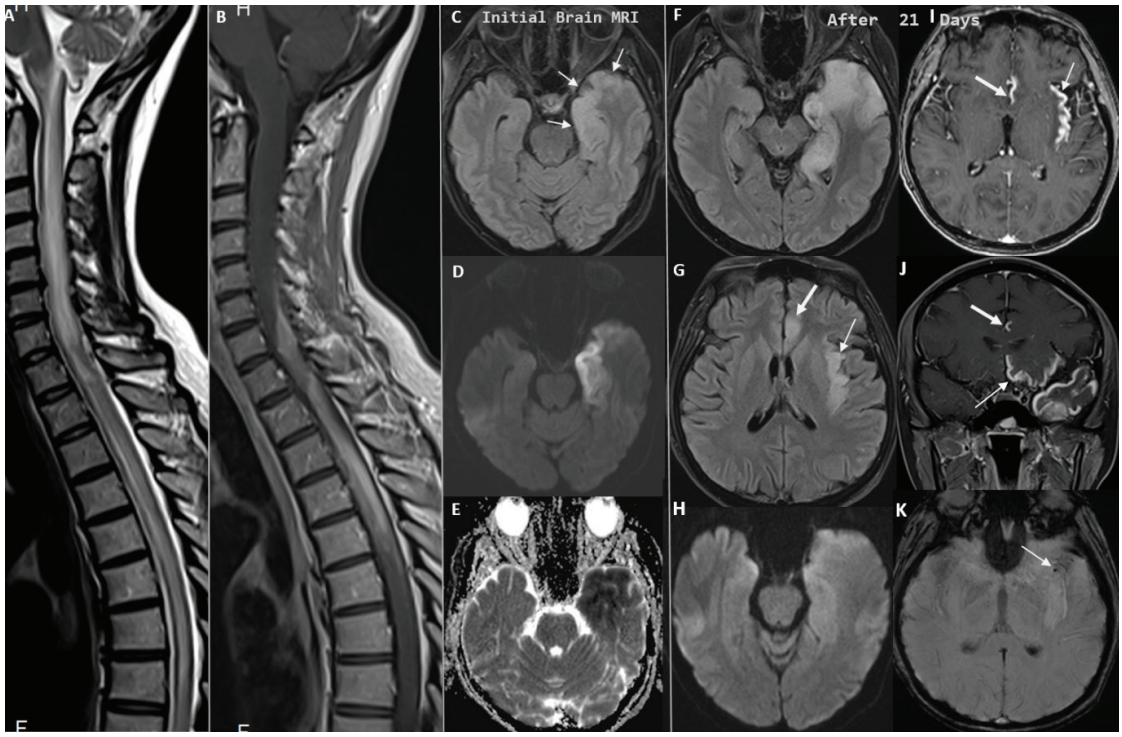

Figure 1. a–k. Sagittal T2W **(a)** and postcontrast T1W **(b)** magnetic resonance (MR) images of the spine shows a longitudinally extending from medulla oblongata to 9th thoracic vertebra level, T2-hyperintense **(a)**, heterogeneously contrast-enhancing **(b)**, and expansile intramedullary lesion. Axial FLAIR MR image **(c)** showing left mesial temporal cortical hyperintensity and swelling *(arrows)*. Diffusion-weighted imaging (DWI)-trace image **(d)** and ADC map **(e)** reveals cytotoxic edema in the lesion. Three weeks after initiation of acyclovir therapy, axial FLAIR **(f, g)** and postcontrast T1W images **(i, j)** demonstrate an increasing extension of the lesion other limbic structures including the cingulate gyrus **(g, i, j,** *thick arrow***)** insula **(g, i,** *thin arrow***)** and basis of the frontal lobe **(i,** *thin arrow***)** and new-onset gyral contrast enhancement. Diffusion-weighted imaging (DWI)-trace image **(h)** showing resolution of the cytotoxic edema. Susceptibility-weighted image **(k)** shows a microhemorrhage in the lesion *(arrow)*.

disorientation. She could speak meaningless one or two-words with repetition and naming disruption. Her motor and sensorial examination showed mild paraparesis, hypoesthesia, and brisk tendon reflexes. Brain MRI demonstrated a T2-hyperintense lesion with cytotoxic edema in the left medial temporal, hippocampal and insular areas suggestive of Herpes encephalitis (HSV, Figure 1. c–e).

We started intravenous (IV) acyclovir treatment for the possible HSV encephalitis. Lumbar puncture was performed, the glucose and protein levels in the CSF were 61 mg/dl (serum: 103 mg/dl), 47 mg/dl, respectively. Oligoclonal band examination was negative again, and cytological examination revealed mild lymphocytosis. Herpes simplex type-1 lgG and HSV PCR type 1 were positive in the CSF analysis. Antibodies for autoimmune encephalitis (NMDAR, AMPA1, AMPA2, CASPR2, LGI1, GABAB) in the CSF was negative. Electroencephalography (EEG) showed periodic epileptiform discharges in the left frontotemporal area. After starting levetiracetam 2000 mg/day and lacosamide 200 mg/day, we observed improvement in the patient`s orientation and speech. She received twenty-one days of IV acyclovir for HSV encephalitis. As her symptoms did not improve, her follow-up brain MRI was performed after acyclovir treatment and showed increased T2 hyperintensity and Gd enhancement in the T1W images on the left limbic area. (Figure 1. f–k) Therefore, we performed a new CSF evaluation. CSF protein level was found to be even higher (102.1 mg/dL). HSV PCR type 1 was found to be negative after acyclovir treatment. The persistence of the symptoms, new MRI findings, and CSF results strongly supported the new diagnosis of anti– NMDAR encephalitis, and this time, the CSF NMDAR antibody was positive.

With the diagnosis of anti-NMDAR mediated autoimmune encephalitis, we started five-day intravenous immunoglobulin treatment (IVIg) (0.4 g/kg) and continued with a weekly 0.4 g/kg regimen. We could not find any abnormalities in the laboratory and radiological scans for underlying malignant process. One month after the IVIG treatment, she was fully oriented and cooperated, and her experienced mild paraparesis. Additionally, we started the rituximab (RTX) treatment for the NMOSD, after observing the stabilization of her viral encephalitis serology. After RTX treatment and controlling of the seizures, her neurologic examination improved. She was able to walk and cooperate in time, space and person.

DISCUSSION

NMOSD are a group of relapsing inflammatory autoimmune CNS diseases, and the descriptive criteria were revised by Wingerchuck et al. in 2006. In essence, absolute criteria are the presence of optic neuritis and myelitis, while supportive criteria are MRI evidence of a contiguous spinal cord lesion (three or more segments in length), CNS lesions not suggestive for MS, and serological evidence of NMO-IgG or anti-AQP4 antibodies (1).

NMOSD with Sjogren coexistence was accepted as a primary diagnosis of our patient. After steroids and plasmapheresis, for maintenance treatment, AZA was offered as the final maintenance option. While our patient was under AZA treatment she applied with partial cooperation, place and time disorientation, and speech difficulty. In the literature, there have been several cases of NMOSD presenting with mental confusion due to diencephalic involvement of the NMOSD or posterior reversible encephalopathy syndrome (PRES) (2). The MRI revealed new involvement of temporal lobes excluding the diagnosis of PRES in NMOSD. Besides, her CSF protein level was higher than the initial CSF protein, and HSV PCR was positive for HSV Type 1. Her final evaluation supported the final diagnosis of HSV encephalitis.

Our case is unique with the coexistence of two CNS autoimmune disorders with the unfortunate presence of HSV encephalitis. In the literature, there have been no case reports of NMO under AZA treatment presenting with HSV encephalitis. However, various HSV cases are using AZA treatment for various diagnoses such as acute lymphoblastic leukemia, Crohn's disease, and breast cancer (3–5). For neurologists, it is essential to follow up on the new symptoms to be aware of the side effects of these immunosuppressive drugs.

Another remarkable point of our case is the presence of NMDAR antibodies after HSV encephalitis. As mentioned above, her initial antibody results were negative. Many authors demonstrated the induction of anti-NMDAR autoimmune encephalitis after herpes encephalitis (6). The time interval between these two diagnoses has been reported approximately as forty days (6). In our patient, this interval was relatively short (26 days) due to the continuation of close monitorization. The presence of movement disorders, psychiatric manifestations, speech dysfunction, autonomic and cognitive dysfunction in an HSV encephalitis patient are highly suggestive of the diagnosis for anti-NMDAR encephalitis (6). The persistence of symptoms, new MRI findings, and the positivity of anti-NMDAR antibody in the CSF confirm the diagnosis.

In our case, the biphasic clinical pattern frequently stated in the literature did not occur. However, clinical improvement was not achieved despite three weeks of acyclovir treatment. Anti-NMDAR– encephalitis followed HSE lack of clinical or radiological improvement period. Control brain MRI showed progression of the lesions. It is challenging to distinguish anti-NMDAR-encephalitis and HSE radiologically, especially early in the course of HSE. However, there are several helpful MRI features useful in differentiation. Hemorrhage, gyral contrast enhancement, and necrosis, which are characteristic features of HSE, are not observed in the early stage as in our case. Fortunately, diffusion restriction is a frequently seen imaging finding in the early stage of HSE. Most patients with NMDAR-encephalitis have not contrast enhancement or abnormal diffusion-weighted images. In patients with anti-NMDAR encephalitis, brain MRI can be normal in approximately 60% of the patients (7). Both can involve limbic systems; but, HSV encephalitis characteristically spares the basal ganglia and is limited to the limbic system, whereas anti-NMDAR encephalitis may also involve extra-limbic regions such as parietal and occipital lobes, thalamus, basal ganglia, corpus callosum, and brain stem (8). In our patient, no involvement was observed in extra-limbic regions during NMDAR antibody positivity. Even if involvement in the limbic system is present, it may be obscured by progressing imaging findings of HSE.

The pathogenesis of HSV encephalitis triggering anti-NMDAR encephalitis has been frequently discussed by other authors (6). The most accepted hypothesis is that the neuronal destruction caused by HSV infection in the CNS may trigger an autoimmune response by exposing the neuronal antigens to systemic immunity and eventuate in the production of anti-NMDAR antibodies (6). Other hypotheses include initiation of the autoimmune response with non-specific B-cell activation due to shared epitopes between HSV and NMDAR (7).

Another interesting characteristic about this case is that it draws attention to the coexistence of NMOSD and anti-NMDAR encephalitis. There are only 11 adult cases in the previous literature that had anti-NMDA encephalitis with NMOSD (9–15). Among those cases, the interval of these two diseases varies between 5–84 months (9–15). The prior disease can be either NMOSD or anti-NMDAR encephalitis. None of them had a known-HSV positivity. With all these features mentioned above, our patient is a representative case mentioning the importance of close follow-up of a patient in neuroimmunology.

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REFERENCES

1. Wingerchuk DM, Lennon VA, Pittock SJ, Lucchinetti CF, Weinshenker BG. Revised diagnostic criteria for neuromyelitis optica. Neurology 2006;66:1485–1489. [Crossref]
2. Poppe AY, Lapierre Y, Melançon D, Lowden D, Wardell L, Fullerton LM, et al. Neuromyelitis optica with hypothalamic involvement. Mult Scler 2005;11:617–621. [Crossref]
3. Cathomas R, Pelosi E, Smart J, Murray N, Simmonds P. Herpes simplex encephalitis as a complication of adjuvant chemotherapy treatment for breast cancer. Clin Oncol (R Coll Radiol) 2005;17:292–3. [Crossref]
4. Robineau O, Enrico J, Lemaire X, Poissy J, Legout L, Senneville E, et al. Herpes simplex virus meningoencephalitis in a patient with Crohn's disease on azathioprine therapy. Am J Gastroenterol 2010;105:240–241. [Crossref]
5. Lauten M, Guttel C, Hartel C, Erdlenbruch B. Herpes simplex virus reactivation and disease during treatment for childhood acute lymphoblastic leukemia. Klin Padiatr 2014;226:188–189. [Crossref]
6. Nosadini M, Mohammad SS, Corazza F, Ruga EM, Kothur K, Perilongo G, et al. Herpes simplex virus-induced anti-N-methyl-d-aspartate receptor encephalitis: a systematic literature review with analysis of 43 cases. Dev Med Child Neurol 2017;59:796–805. [Crossref]
7. Titulaer MJ, McCracken L, Gabilondo I, Armangué T, Glaser C, Iizuka T, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol 2013;12:157–165. [Crossref]
8. Zhang T, Duan Y, Ye J, Xu W, Shu N, Wang C, et al. Brain MRI Characteristics of Patients with Anti-N-Methyl-D-Aspartate Receptor Encephalitis and Their Associations with 2-Year Clinical Outcome. AJNR Am J Neuroradiol 2018;39:824–829. [Crossref]
9. Qin K, Wu W, Huang Y, Xu D, Zhang L, Zheng B, et al. Anti-N-methyl-D-aspartate receptor (NMDAR) antibody encephalitis presents in atypical types and coexists with neuromyelitis optica spectrum disorder or neurosyphilis. BMC Neurol 2017;17:1. [Crossref]
10. Tao S, Zhang Y, Ye H, Guo D. AQP4-IgG-seropositive neuromyelitis optica spectrum disorder (NMOSD) coexisting with anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis: A case report and literature review. Mult Scler Relat Disord 2019;35:185–192. [Crossref]
11. Fan S, Xu Y, Ren H, Guan H, Feng F, Gao X, et al. Comparison of myelin oligodendrocyte glycoprotein (MOG)-antibody disease and AQP4-IgG-positive neuromyelitis optica spectrum disorder (NMOSD) when they co-exist with anti-NMDA (N-methyl-D-aspartate) receptor encephalitis. Mult Scler Relat Disord 2018;20:144–152. [Crossref]
12. Zoccarato M, Saddi MV, Serra G, Pelizza MF, Rosellini I, Peddone L, et al. Aquaporin-4 antibody neuromyelitis optica following anti-NMDA receptor encephalitis. J Neurol 2013;260:3185–7. [Crossref]
13. Ran Y, Wang L, Zhang F, Ao R, Dong Z, Yu S. Anti-NMDAR encephalitis followed by seropositive neuromyelitis optica spectrum disorder: A case report and literature review. Clin Neurol Neurosurg 2017;155:75–82. [Crossref]
14. Luo J-J, Lv H, Sun W, Zhao J, Hao H-J, Gao F, et al. Anti-N-methyl-d-aspartate receptor encephalitis in a patient with neuromyelitis optica spectrum disorders. Mult Scler Relat Disord 2016;8:74–77. [Crossref]
15. Titulaer MJ, Höftberger R, Iizuka T, Leypoldt F, McCracken L, Cellucci T, et al. Overlapping demyelinating syndromes and anti-N-methyl-D-aspartate receptor encephalitis. Ann Neurol 2014;75:411–428. [Crossref]